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(54) Immuno-tolerant stent with surface microstructure

(57) The current concept aims towards to modify the immuno response by inducing a immuno tolerance with two factors: 1. Modifying the stent surface with a surface characteristic in a range of 1 - 5 µ, that is considered to be not foreign for the body and 2. to add small traces to immuno suppressant drug. With this concept the wound healing is facilitated without suppressing the normal wound-healing but the prolonged re-stenotic proliferation is avoided. Only small traces of an immuno suppressant drug locally are required, preferably the drug is applied without a carrier to the surfaces. The use of a biodegradable or non-biodegradable is feasible as well.

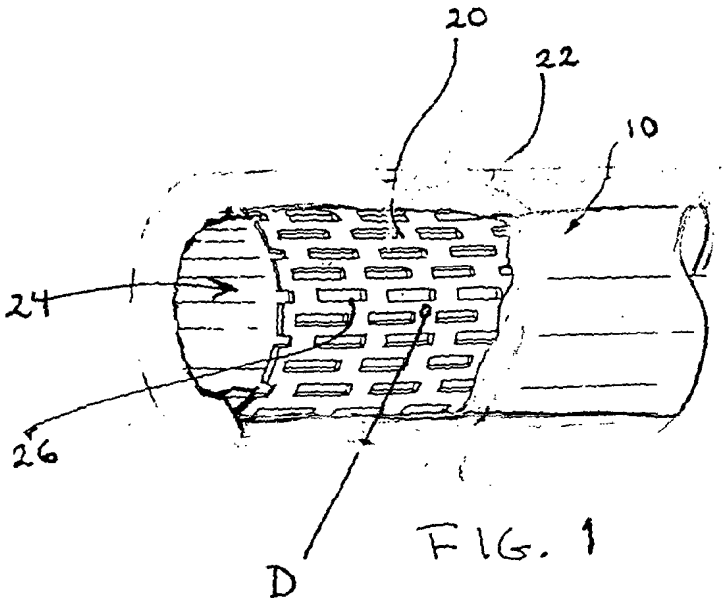

FIG. 1

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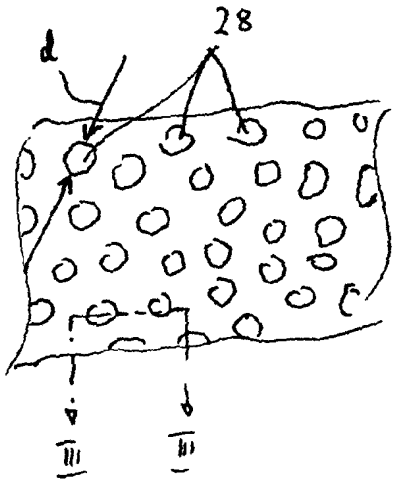

Fig. 2

Description

[0001] The invention refers to a stent according to the preamble of claim 1.

[0002] Stents are widely used to support a lumen in the human body, especially the lumen of a coronary artery.

[0003] The problem of coronary restenosis has been one of the major challenges for modern interventional cardiology.

[0004] Despite major progress in stent design, stent technology, flexibility, delivery systems and other means to improve the technique of coronary stenting, coronary restenosis still is of concern. Roughly 25% of all patients which receive an intervention in their vascular bed receive an implant and suffer a restenosis, which means that more than 50% of the initial lumen gain are lost in the follow-up between 6 weeks and 6 months.

[0005] A wide range of solutions have been proposed including a modification of the stent surface by iridiumoxide or the coating of the stent surface with biodegradable or non-biodegradable coatings. It has been proposed to provide the stent surface with a coating of an immuno suppressing drug, namely "Tacrolimus", which prevents or at least reduces the immuno-response by a modification of the immuno-response of the body. These drugs are otherwise used to suppress the rejection of transplants in the human body. In addition, recent research has shown, that a rough stent surface may be advantageous to prevent restenosis. However, precise predictions and results could not be achieved as yet.

[0006] It is an object of the present invention to propose a stent, which maximizes the benefit as far as the immuno-reaction by the body against the implanted foreign body is concerned.

[0007] This object is solved by the features of claim 1.

[0008] Further embodiments and advantages of the invention are disclosed in the subclaims.

[0009] The solution is, to minimize the surface recognition of the stent as an implanted foreign bod by creating a stent surface, which is more immuno tolerant than a smooth or generally rough surface. It has shown, that the stent restenosis primarily is a foreign body recognition with concomitant inflammatory reaction against the implanted foreign body, very similar to the rejection of a transplanted organ with a foreign body surface to the body. This reaction primarily is brought forward by T-Lymphocytes. These Lymphocytes attack anything which is determined to be foreign and a release of Cytokines is affected following this recognition.

[0010] It could be shown, that the reaction to a transplanted foreign body is minimized, if a certain stent surface structure can be achieved which mimics the surface structure of the patient's own cells. By applying a surface structure of the stent having microstructures with lateral dimensions in the range of o.5 to 5 micrometers (μm) and espaecially 1 to 3 μm roughness, the body is blinded towards the foreign body and by surface characterization and immuno tolerance is induced.

[0011] This is absolutely in contrary to the current opinion that a stent surface should be smooth in order to be well tolerated by the human body. The experiment, that has been conducted at applicants research lab, has shown, that especially a structure with an inert material, such as iridiumoxide, niobiumoxide, titaniumnitrate or other very inert ceramic-like structures, suppress this immuno-reaction.

[0012] In addition, small traces of the immuno modulating drug "Tacrolimus" or "Sirolimus" enhance the action towards a suppressed immuno reaction.

[0013] The consequences of this blinding of the immuno response by especially two factors, surface modification and in addition the adding of small traces of an immuno suppressing drug without any systemic effect, promote the healing of the stent without suppressing the proliferation of smooth muscle cells.

[0014] A problem of all currently proposed concepts with drugs was the assumption that only the inhibition of the proliferation would be sufficient to suppress restenosis. In contrary thereto, the aim of this invention is to allow the proliferation of smooth muscle cells to the same degree as they normally would proliferate, but suppress the continuous overshooting proliferation that goes beyond the wound healing. This overshooting proliferation is responsible for the restenosis and is based on an inflammatory response toward the foreign body which is recognized by the T-cell system.

[0015] The combined approach of blinding the recognition of the implanted foreign body by grading a structure in a range of 1 to 5μm, especially 1 to 3μm, by additionally using material that has very inert surface properties, has no release of toxic substances, has a positive surface charge in the range 30 to 50 dynes/cm (g x cm x s^{-2}/cm), which reduces fibrinogen adhesion, that also diminishes the inflammatory reaction towards the release of metallic salts from otherwise stainless steel, which is especially avoided by an inert ceramic-like structure, all these factors contribute to the diminished immuno response.

[0016] The additional application of an immuno suppressive drug such as Sirolimus or Tacrolimus helps to overcome the still ?, but very weak inflammatory response toward such an implanted foreign body, which is not only due to the surface recognition, but also to the mechanical trauma which is brought forward by the implantation of the stent.

[0017] The application of the immuno drug can be effected ether by dipping the stent in a solution of the drug. For example, 40 mg Tacrolimus are dissolved in 6 ml of Chloroform or Ethylacetate and on the stent surface soaked by adhesion forces and by capillary forces the drug into the surface coating. The stent is taken out of the solution and the solvent evaporates following the high pressure of the dissolved chloroform into the ambient atmosphere rapidly. The consequence is, that de-

pendent on the initial concentration small traces of the drug are bound to the surface and soaked into the network, the grooves and the capillaries of the rough surface structure of the stent.

[0018] Thereby, the surface modification of the stent serves two purposes:

1. It blinds the recognition of the stent surface as a foreign body and

2. it facilitates and helps to retain traces in a range of 5 - 50 µg of immuno drug on the surface structure of the stent.

[0019] In addition the application of the drug by means of a biodegradable or non-biodegradable carrier can be done as well. So drugs had been described previously and are consisting of ether biodegradable such as polylactic acid or non-biodegrable or non-erodable polymers such as polyurethane, polyvinylacetate or other.

[0020] Further details and advantages of the present invention are disclosed in the following description in connection with the annexed drawings, in which.

Fig. 1 is a perspective partial view of a stent according to the invention;

Fig. 2 is a schematic view of a part D of the surface of the stent: and

Fig. 3 is a section according to line III - III in Fig. 2.

[0021] **Fig. 1** shows a part of a stent **10** in form of a small tube **20** preferably made of a niob-zirconium alloy which has two open ends (one is shown at **24)** and a lot of openings **26** in the wall of the tube **20,** so that the stent may be crimped on an angioplasty balloon (not shon) and deployed by the balloon on a treatment site for example in a coronary artery from its shown first small diameter to a second greater diameter so that the outer surface of the stent is in contact with the inner wall surface of the artery. Many designs of the stent are possible and well known in the state of the art; for the invention the configuration of the stent is not relevant.

[0022] The outer surface of the stent **10** is modified and provided with small protrusions or microstructures **28** as shown in **Figs. 2** and **3** for a small region **D** depicted in **Fig. 1.** These microstructures have a lateral extension **d** in the range of 0.5 to 5 micrometers, preferably in the range of 1 to 3 micrometers. The spacing **e** between adjacent microstructures is in the same range as schematically shown in **Fig. 3.** The height **h** of the microstructures between the peak of a microstructure and the valley adjacent to a next microstructure may have a lower value and lie in the range of 0.5 to 2 micrometers.

[0023] The microstructures **28** may be a coating **30** of a ceramic-like material such as iridiumoxide, which may be deposited on the surface of the surface of the stent by means of plasma or chemical vapour deposition or the like.

[0024] The microstructures **28** may have the form of microspheres or parts thereof; the surface of the microstructures may not be smooth and be provided with grooves or furrows **32** depending on the manufacturing process.

[0025] The stent is then dipped into a solution of an immuno suppressing drug, for example "Tacrolimus" or "Sirolimus", and a solvent such as chloroform, so that the solution covers the surface of the stent, partially by capillary forces in the region of the grooves **32.** The stent is then more or less covered by a coating **34** of the immuno suppressing drug.

Claims

1. A stent for implantation in a lumen of the human body, the stent being expandable from a first small diameter to a second greater diameter, at which the stent is in contact with the inner surface of the lumen to hold the lumen open, whereby the stent is provided with a rough outer surface, **characterised in that** the surface of the stent is realised by microstructures separated from each other and having lateral dimensions in the range of 0.5 to 5 micrometers, whereby the recognition of the stent as an implanted foreign body is reduced.

2. Stent according to claim 1, **characterised in that** the lateral dimensions of the microstructures are in the range of 1 to 3 micrometers.

3. Stent according to claim 1 or 2, **characterised in that** the lateral distance between the microstructures from each other is in the range of 0.5 to 5 micrometers, especially 1 to 3 micrometers.

4. Stent according to one of the preceding claims, **characterised in that** the distance between the peaks and the valleys of adjacent microstructures is in the range of 0.5 to 5 micrometers, especially 0.5 to 2 micrometers.

5. Stent according to one of the preceding claims, **characterised in that** the surface structure of the stent is inert and releases no toxic substances.

6. Stent according to one of the preceding claims, **characterised in that** the surface structure of the stent has a surface charge in the range of 30 - 50 dynes/cm (g x cm x s^{-2}/cm).

7. Stent according to one of the preceding claims, **characterised in that** the stent is additionally provided with an immuno suppressing drug to treat the

inner surface of the lumen and to prevent an immuno reaction thereof.

8. Stent according to claim 7, **characterised in that** the immuno suppressing drug is dissolved in a solvent and applied to the roughened surface of the stent by the capillary forces of the surface structure of the stent.

9. Stent according to claim 7, **characterised in that** the immuno suppressing drug adheres on the surface of the stent following the capillary forces without using a carrier.

10. Stent according to one of claims 7 to 9, **characterised in that** the addition of the immuno suppressing drug is realised by using the capillaries and grooves of the surface structure of the stent to retain the immuno suppressing drug on said surface.

11. Stent according to one of the preceding claims 7 to 10, **characterised in that** the drug is able to suppress an immuno reaction or response interacting with the T-cells of the human body.

12. Stent according to one of the preceding claims 7 to 11, **characterised in that** the immuno suppressing drug is sirolimus

13. Stent according to one of the preceding claims 7 to 11, **characterised in that** the immuno suppressing drug is tacrolimus.

14. Stent according to one of the preceding claims, **characterised in that** the surface of the stent modified by the microstructures is made of iridiumoxide.

15. Stent according to one of the preceding claims 1 to 13, **characterised in that** the surface of the stent modified by the microstructures is made of niobiumoxide.

16. Stent according to one of the preceding claims 1 to 13, **characterised in that** the surface of the stent modified by the microstructures is made of Titaniumnitrate.

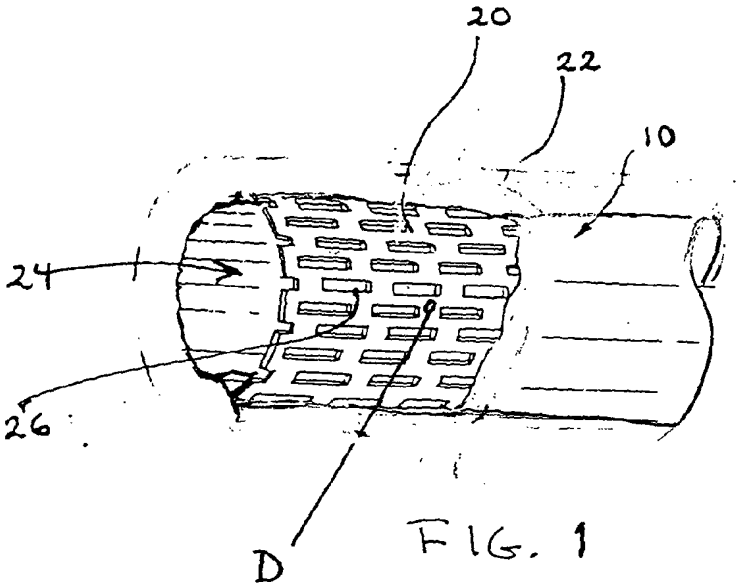

FIG. 1

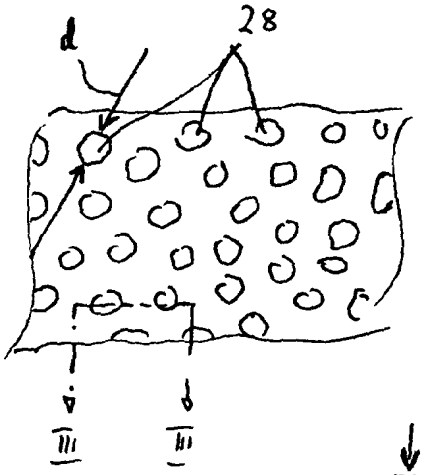

Fig. 2

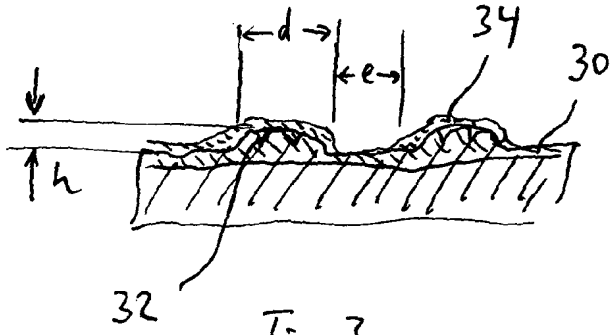

Fig. 3

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EUROPEAN SEARCH REPORT

Application Number
EP 01 13 1051

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TECHNICAL FIELDS SEARCHED (Int.Cl.7)

A61L

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	22 August 2002	Heck, G

CATEGORY OF CITED DOCUMENTS

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